REMARKS

Claims 76-116 and 118-127 presently appear in this case. Claims 76-107 have been withdrawn from consideration. No claims have been allowed. The Official Action of October 27, 2009, has now been carefully studied. Reconsideration and allowance are respectfully urged.

The present invention is based on the finding that sphingoid polyalkylamine conjugates, such as N-palmitoyl D-erythro sphingosyl carbamoyl-spermine (CCS), provide enhancement of the extent and nature of the immune response to an antigen. As such, the sphingoid polyalkylamine conjugates act as adjuvants.

The adjuvanticity of the sphingoid polyalkylamine conjugate is supported throughout the specification. Specifically, when referring to the Examples, it is shown that HI titers induced with formulations comprising the sphingoid polyalkylamine conjugate, CCS, were significantly higher than those obtained with other liposomal formulations or even with liposomal formulations comprised of many other positively charged lipids.

For instance, Table 2A shows that formulation 10, comprised of liposomes comprising CCS as the N-palmitoyl D-erythro sphingosyl carbamoyl-spermine and HN as the antigen (Lip(CCS:Chol)-HN), induces a much higher HI titer and IgG2a

level than any other formulation tested (formulations 5-10 all being different cationic liposomes carrying the same antigen). A similar difference with respect to HI titer is exhibited in lung and nasal wash levels (formulation 10 in Table 2B, formulations 12-16 in Table 3B, formulation 10 in Table 4B). Also, Spleen INFγ levels are also much higher with Lip(CCS:Chol)-HN (formulation 10 in Table 2C, and formulations 10 and 11 in Table 4C).

Furthermore, the superiority of CCS as the cationic lipid in the liposome is exhibited, *inter alia*, in Table 6, relating to the induction of cellular immune responses by various cationic liposomes administered intranasally, including Lip(CCS:Chol)-HN.

One might have thought on the first level that the difference in charge of lipid (positive vs. neutral vs. negative) would be the primary factor in the adjuvanticity of formulations with sphingoid polyalkylamine conjugates. One might further rationalize on this level that this observation on adjuvanticity is due to the expectation that positively charged liposomes would be more naturally attracted electrostatically to the negatively charged surface, hence mediating more effective delivery of the antigen for cellular processing and immune stimulation. However, this argument does not explain on a second level why sphingoid

polyalkylamine conjugates, such as CCS, mediate superior adjuvanticity compared to other positively charged lipids in liposomal formulations. Therefore, the superior adjuvanticity of sphingoid polyalkylamine conjugates is unexpected and surprising, which reinforces its novelty and non-obviousness to those skilled in the art.

The adjuvanticity of N-palmitoyl D-erythro sphingosyl carbamoyl-spermine exemplified by Lip (CCS:Chol)-HN is specifically stated, *inter alia*, at the following passages of the present specification. On page 22, lines 1 to 7:

> The superiority of Lip CCS-HN vaccine over the other vaccine formulations is again seen as reflected by the high level of serum and lung IgG2a and IgA antibodies … This suggests that real encapsulation of the antigen may not be necessary for the adjuvanticity of the cationic assemblies/liposomes.

On page 25, lines 15-16:

> Moreover, whereas DMTAP-HN elicits a strong humoral response, this formulation is a poor inducer of cytotoxic activity as compared with CCS-HN.

And also on page 43, lines 8-11:

> These findings combined with the long retention of the CCS-flu vaccine in the respiratory tract (Fig. 2C and 2F and Fig. 3A-3D) after intranasal administration may explain why CCS is such an efficient mucosal vaccine carrier/adjuvant.

And on page 43, lines 26-28:

> Thus, CCS lipid assemblies alone, and particularly in combination with CpG-ODN, are also effective as a carrier/adjuvant for mucosal vaccination against HAV.

Thus, to summarize, use of sphingoid polyalkylamine conjugates in accordance with the invention is not only acting as a simple carrier for biologically active molecules, as contended by the examiner, but in fact is also acting as an adjuvant.

In the Official Action of October 27, 2009, the restriction requirement was deemed proper and made final. However, as it will be shown below that the product claims are allowable, it would now be appropriate to rejoin the method of use claims. This must be done once the existence of a special technical feature has been established.

Claims 118-127 have been rejected under the second paragraph of 35 USC 112 as claim 118 recites a dependency from a cancelled claim. The examiner has interpreted claim 118 as if it depended from independent claim 108.

Claim 118 has now been amended to correct its dependency so that it now depends from claim 108, as properly assumed by the examiner. It is appreciated that the examiner anticipated this correction when considering this claim on the merits.

Claims 108-114 have been rejected under 35 USC 103(a) as being unpatentable over Jorgensen. The examiner

states that Jorgensen teaches a composition comprising a lipid-polyalkylamine conjugate, and particularly the claimed sphingoid-polyalkylamine conjugate. The examiner recognizes, however, that Jorgensen does not include a biologically active molecule with the composition. However, the examiner states that the compound of Jorgensen can be used to facilitate delivery of therapeutic agents such as DNA, mRNA, antisense oligonucleotides, proteins and drugs into cells - all of which are allegedly biologically active molecules that modulate and induce an immune response, citing page 1 of Jorgensen. The examiner states that one of ordinary skill in the art, at the time the invention was made, would have been motivated to combine them to facilitate delivery of molecules, and that one of ordinary skill in the art would have had a reasonable expectation of success for doing so because Jorgensen discloses that lipid-polyalkylamine conjugates are effective to facilitate delivery of drugs into cells. This rejection is respectfully traversed.

In order to better define the present invention over Jorgensen, claim 108 has now been amended to specify that the biologically active molecule is "an immune response modulating biologically active molecule" and that the amount of sphingoid polyalkylamine conjugate is effective to enhance activity of said biologically active molecule on the immune response of

the subject. This is an activity not recognized by Jorgensen and establishes unexpected results that rebut any *prima facie* case of obviousness that may have been established by the examiner. Jorgensen does not teach or suggest that a sphingoid polyalkylamine conjugate will enhance the activity of an immune response modulating biologically active molecule on the immune system of a subject. All the more, the superiority of the sphingoid polyalkylamine conjugate according to the invention over other liposomal formulations in providing such enhancement could not have been taught or deduced from the disclosure of Jorgensen.

The examiner takes the position that the use of a sphingoid polyalkylamine conjugate as a carrier to transfer proteins, drugs and DNA into cells will modulate and induce the immune response. However, this statement is incorrect and is not supported by any evidence of record. The first paragraph of Jorgensen says that the compound is useful in gene therapy. Gene therapy does not necessarily involve the immune system. The biologically active molecule claimed in claim 108 must be one which is an immune response modulating biologically active molecule and which can be administered in an amount "effective to modulate the immune response of a subject." Not every protein and drug has that capability. The present claim is to a vaccine. A vaccine is a biological

preparation that improves immunity to a particular disease. The typical use suggested for the compound of Jorgensen merely transfers a biologically active material to the inside of a cell. It is not a vaccine and the immune system is not affected by such a transfer. Thus, the mention of transferring a drug into a cell does not inherently make obvious the combination of the sphingoid-polyalkylamine conjugate with an immune response modulating biologically active molecule. The deliver of such a molecule into a cell is not necessary for its immunomodulatory effect.

The present rejection is an obviousness rejection, not an anticipation rejection. Unexpected properties will rebut a *prima facie* case of obviousness. As discussed above, the compounds of the present surprisingly act as an adjuvant with such vaccines. They even work better than other cationic lipids. The effect is not just the effect of delivery into cells. The effect is special for this particular type of molecule and is surprising.

As Jorgensen does not suggest the adjuvanticity of the sphingoid polyalkylamine conjugate according to the invention, its combination with a biologically active material effective to modulate the immune response of a subject cannot be obvious. Reconsideration and withdrawal of this rejection

insofar as it relates to claim 108 and all claims dependent therefrom are therefore respectfully urged.

Claim 110 is also particularly unobvious from any reading of Jorgensen. It is only obvious to use an adjuvant with a vaccine. There would be absolutely no motivation to use an adjuvant in gene therapy or in any other therapeutic modality in which a molecule is being delivered into a cell. Applicant challenges the examiner's unsupported statement on page 5 of the official action that "the use of adjuvants with therapeutic agents such as biologically active molecules is routinely practiced in the art." The examiner's attention is invited to MPEP 2144.03C, whose heading is:

> C. If Applicant Challenges a Factual Assertion as Not Properly Officially Noticed or Not Properly Based Upon Common Knowledge, the Examiner Must Support the Finding With Adequate Evidence

Adjuvants are only used with vaccines. There is no suggestion in Jorgensen that the compositions used therein would have any use in a vaccine. Reconsideration and withdrawal of this rejection insofar as it relates to claim 110 is also respectfully urged.

Claims 108-116 and 118-127 have been rejected under 35 USC 103(a) as being unpatentable over Miller in view of Jorgensen. The examiner states that Miller teaches a composition comprising cholesterol carbamoyl spermine and its

analogs. The examiner considers it obvious from Jorgensen to use ceramide as the lipid in the lipid-polyalkylamine conjugate of Miller and to use it to facilitate delivery of therapeutic agents into cells. This rejection is respectfully traversed.

Miller adds nothing to the deficiencies of Jorgensen as discussed with respect to claims 108 and 110. Accordingly, the combination of Jorgensen with Miller still does not establish the obviousness of use of the sphingoid-polyalkylamine conjugate with a biologically active molecule capable of modulating the immune system of a subject, or the unexpected adjuvant effect of the compound on that immunomodulation. Accordingly, reconsideration and withdrawal of this rejection for the same reasons as discussed above with respect to the rejection over Jorgensen alone, are respectfully urged.

Additionally, claim 116 should be considered in its own right. There would be no known reason to deliver a molecule derived from influenza virus into a cell. Thus, it would not be obvious to use this molecule as the biologically active molecule of Jorgensen or Miller, even in accordance with the examiner's strained interpretation of the molecules that are allegedly obvious to use with the compounds of Jorgensen or Miller (or combination). This claim is to a flu

vaccine. The vaccine of claim 116 has unexpected properties as the sphingoid-polyalkylamine conjugate acts as an adjuvant. The prior art certainly does not suggest this. Thus, claim 116 is allowable in its own right. Reconsideration and withdrawal of this rejection insofar as it relates to claim 116 is therefore also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and are in full compliance with 35 USC 112. Accordingly, reconsideration and allowance are earnestly solicited.

Respectfully submitted,

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